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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/884,465 | 06/20/2001 | Josee Hamel | 55190-044 | 9640 |

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| EXAMINER | |
|---|---|
| FORD, VANESSA L | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1645 | |

DATE MAILED: 12/01/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/884,465 | HAMEL ET AL. | |
| | Examiner | Art Unit | |
| | Vanessa L. Ford | 1645 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *13 September 13, 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *18,19,25,35 and 36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *19* is/are allowed.

6)☒ Claim(s) *18,25 and 34-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on September 13, 2004 has been entered. Claims 1-17, 20-24 and 26-33 have been cancelled. Claim 19 has been amended. Claims 35 and 36 have been added.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in the prior Office Action.

### *Rejections Withdrawn*

3. In view of Applicant's amendment and response the following rejections are withdrawn:

a) rejection of claims 18-19, 25 and 34 35 U.S.C. 112, first paragraph (written description) on pages 3-5 of the Final Office Action.

b) rejection of claims 18-19 and 25 35 U.S.C. 112, second paragraph on page 7, paragraph 5 of the Final Office Action.

***Rejections Maintained***

4. The rejection under 35 U.S.C. 112, first paragraph (enablement) is maintained for claims 18, 25 and 34 for the reasons set forth on pages 5-7 of the Final Office Action.

The claims are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated *Streptococcus pneumoniae* polypeptide that has the amino acid sequence as set forth in SEQ ID NO: 332 (elected sequence), does not reasonably provide enablement for polypeptides having about 85% sequence similarity to SEQ ID NO: 332.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The encompass amino acid sequences that correspond to sequences from other species, mutated sequences, allelic variants, splice variants, sequences that have a recited degree of identity (similarity, homology), and so forth. The specification teaches that the antigenic/immunogenic fragments of invention include one or more epitopic regions (page 15). The specification does not disclose, which amino acids are involved in the claimed epitope bearing portions of the *Streptococcus pneumoniae* polypeptide as set forth in SEQ ID NO:332 nor does the specification provide guidance as to how many location changes (i.e. deletions) can be used to produce an epitope bearing portion of SEQ ID. NO:332. No working examples are shown containing the missing information. There is no guidance provided as to which amino acids can be deleted and

still have the polypeptides retain its biological function. The specification provides essentially no guidance as to which of the essentially infinite possible choices is likely to be successful. Without such information, one of skill in the art could not predict which deletions, would result in the desired polypeptide.

The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of proteins broadly encompassed by the claims and the claims broadly encompass a significant number of inoperative species. Since the amino acid sequence of the protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and still retain similar activity requires a knowledge with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expected intolerant to modification) and detailed knowledge of the ways in which the protein's structure relates to function. However, the problem of the prediction of protein's structure from mere sequence data of a single protein and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein and finally what changes can be tolerated with respect thereto is extremely complex and outside of the realm of routine experimentation.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen multiple substitutions or multiple modifications of other types and the positions within the protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining similar activity are limited in any polynucleotide and the result of such modifications is unpredictable based on the instant

disclosure. One skilled in the art would expect any tolerance to modifications, e.g., multiple substitutions. The sequence of some proteins is highly conserved and one skilled in the art would not expect tolerance to any amino acid modification in such protein.

*Thomas E. Creighton, in his book, "Proteins: Structures and Molecular Properties, 1984", (page 315)* teaches that variation of the primary structure of a protein can result in an instable molecule. He teaches that a single amino acid change can cause a mutant hemoglobin to have lower stabilities due to any of several causes: 1) alteration of close-packing of the interior; loss of one group that normally participates in a hydrogen bond or salt bridge; 2) the introduction of a charged or polar group into the interior or the insertion into a helical region of a proline residue, which must distort the alpha-helix; 3) while sometimes radical changes of surface groups, even introduction of a non-polar side chain- have no great effect on stability.

*Thomas E. Creighton, in his book "Protein Structure: A Practical Approach, 1989; pages 184-186"* teaches that present day site directed mutagenesis of a gene allows any amino acids in a protein sequence to be changed to any other, as well as introducing deletions and insertions". The reference goes on to teach that it is difficult to know which amino acid to change and which is the best residue to substitute for the desired functional and structural effect.

*Nosoh, Y. et al in "Protein Stability and Stabilization through Protein Engineering, 1991" (chapter 7, page 197, second paragraph)* adds support to Thomas E. Creighton, by teaching that results so far accumulated on the stability and stabilization of proteins

appear to indicate that the strategy for stabilizing proteins differ from protein to protein and that any generalized mechanisms for protein stability have not yet been presented.

Since the amino acid sequence of the protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and still retain similar activity requires a knowledge with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expected intolerant to modification) and detailed knowledge of the ways in which the protein's structure relates to function. However, the problem of the prediction of protein structure from mere sequence data of a single protein and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein and finally what changes can be tolerated with respect thereto is extremely complex and outside of the realm of routine experimentation.

Factors to be considered in determining whether undue experimentation is required, are set forth in In re Wands 8 USPQ2d 1400. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims.

Applying the above test to the facts of record, it is determined that 1) no declaration under 37 C.F.R. 1.132 or other relevant evidence has been made of record establishing the amount of experimentation necessary, 2) insufficient direction or guidance is presented in the specification with respect to epitope bearing portions of a

polypeptide has an amino acid sequence as set forth in SEQ ID NO:332 having claimed functional features, 3) the relative skill of those in the art is commonly recognized as quite high (post-doctoral level). One of skill in the art would require guidance, in order to make of the claimed *Streptococcus pneumoniae* polypeptide in a manner reasonable in correlation with the scope of the claims. Without proper guidance, the experimentation is undue.

The Applicant has not provided sufficient guidance to enable one of skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any number of deletions and epitopes of any size. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970). Without such guidance, the changes which can be made in the protein's structure and still maintain activity is unpredictable and the experimentation left those skilled in the art is unnecessarily and improperly, extensive and undue. See Amgen Inc v Chugai Pharmaceutical Co Ltd. 927 F 2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991) at 18 USPQ2d 1026-1027 and Exparte Forman, 230 U.S. P.Q. 546(Bd. Pat=. App & int. 1986).

In view of all of the above, in view of the lack of predictability in the art, it is determined that it would require undue experimentation to make and use the claimed invention commensurate in scope with the claims.

*Response Applicant's arguments filed September 13, 2004.*

Applicant urges that Example 12 of application 09/471,255 describes the cloning and expression of a chimeric gene encoding for a chimeric polypeptide corresponding to the 3' carboxyl-terminal region of BVH03 in fusion at the C' end to the carboxy-terminal region of BVH-11. Applicant urges that Example 12 of application 09/471,255 describes the additive protection observed after vaccination of an animal which a chimeric polypeptide of the present claim. Applicant urges that it is clear from the studies in the present application that BVH-3 and BVH-11 are serologically distinct molecules and simultaneously present on *S. pneumoniae*. Applicant urges that constructs can be made to have any degree of similarity to SEQ ID NO:332, including 85 similarity to SEQ ID NO:332 and various polypeptide fragments of BVH-3 and BVH-11 have been shown to confer an immunoprotective response.

Applicant's arguments filed September 13, 2004 have been fully considered but they are not persuasive. The specification fails to provide enablement for the claimed genus of polypeptides that have 85% similarity to the elected sequence (SEQ ID NO. 332). Although the specification teaches polypeptides that have similarity to BVH-3 and BVH-11 (which are the two components of the chimeric polypeptide) does not provide enablement for polypeptides that are 85% similar to the elected sequence (SEQ ID NO.332). It should be remembered that the claims are directed to isolated polypeptides that have at least 85% similarity to SEQ ID NO: 332 and not a method of preparing or producing polypeptides that have at least 85% identity to SEQ ID NO:332. 35 U.S.C.

112, first paragraph requires the specification teach or disclose how to make and use the claimed invention. It does not require that the specification teach or disclose how one skilled in the art can "find" or "screen for" polypeptides that have 85 % similarity to SEQ ID NO:332 wherein the polypeptide elicits an immune response when administered to an individual. To address Applicant's comments regarding Application 09/471,255, this application has no bearing on the patentability of any claimed invention in the present application. The instant application does not claim priory to Application 09/471, 255. It should be remembered that the present applicant must teach or disclose support for the claimed invention. The instant application does not disclose how one skilled in the art can make and use the claimed invention. How would the skilled artisan begin choosing polypeptides that have at least 85% similarity to SEQ ID NO:332 that elicit an immune response when administered to an individual without guidance. The art cited above teaches the unpredictability of the art regarding single or multiple modifications within an amino acid sequence. How would one skill in the art know which amino acids can be deleted, inserted or substituted within the claimed amino acid sequence and no have a detrimental effect on the claimed polypeptide? A single modification can result in an amino acid sequence that does not retain the desired biological function. The specification must teach or disclose the specific locations in which these modifications can be made. In the absence of such support the experimentation to arrive at the claimed invention is undue. Therefore, the above rejection is maintained.

5. The rejection under 35 U.S.C. 112, second paragraph is maintained for newly presented claim 36 for the reasons set forth on page 7, paragraph 6 of the Final Office Action.

The rejection was on the grounds that the claims are indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 36 recites "susceptible to". It is unclear as to what Applicant is referring. Applicant urges that this rejection is moot in view of the amendment. It is the position of the Examiner that newly submitted claim 36 is indefinite as described above. Clarification is required.

***New Grounds of Rejection***

***Specification***

6. The specification of objected to for the following informality. Figure descriptions (pages 4-6) should have a period (.) at the end of the sentence. Correction is required.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 18, 25, 34 and 35-36 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claimed invention is directed to vaccines and methods of treating and preventing *Streptococcus* infections. The term "vaccine" encompasses the ability of the specific antigen to induce protective immunity to infection or disease induction. The specification does not provide substantive evidence that the claimed vaccines are capable of inducing protective immunity. This demonstration is required for the skilled artisan to be able to use the claimed vaccines for their intended purpose of treating or preventing streptococcal infections. Without this demonstration, the skilled artisan would not be able to reasonably predict the outcome of the administration of the claimed vaccines, i.e. would not be able to accurately predict if protective immunity has been induced. The ability to reasonably predict the capacity of a single bacterial immunogen to induce protective immunity from *in vitro* antibody reactivity studies is problematic. Ellis (*Vaccines, W.B. Saunders Company, Chapter 29, 1988, pages 568-574)*

exemplifies this problem in the recitation that "the key to the problem (of vaccine development) is the identification of the protein component of a virus or microbial pathogen that itself can elicit the production of protective antibodies"(page 572, second full paragraph). Unfortunately, the art is replete with instances where even well characterized antigens that induce an *in vitro* neutralizing antibody response fail to elicit *in vivo* protective immunity. See Boslego et al *(Vaccines and Immunotherapy, 1991, Chapter 17),* wherein a single gonococcal pillin protein fails to elicit protective immunity even though a high level of serum antibody response is induced (page 212, bottom of column 2). Accordingly, the art indicates that it would require undue experimentation to formulate and use a successful vaccine without the prior demonstration of vaccine efficacy.

The specification discloses in Example 7 of the instant specification describes the immunization of animals with peptide epitopes of BVH03 and BVH-11. However, the specification fails to disclose the results of the immunizations. Although the specification teaches that the chimeric polypeptide as set forth in SEQ ID NO: 332 is made up of New 60 (SEQ ID NO: 293) and New 56 (SEQ ID NO:357) which correspond to the BVH-11-2 and BVH-3, respectively, the specification fails to teach or disclose data that demonstrates that the claimed vaccines can provide protection against infections caused by any or all streptococcal infections. There is no disclosure of subjects that have been immunized with the claimed vaccines nor is there a disclosure of challenge studies that have been conducted to established the claimed vaccines ability to provide protection against any or all streptococcal infections.

The claims are also directed to a method of treating and preventing *Streptococcus* infections which encompasses the treatment and/or prevention of all *Strepococcus* infection across the whole *Streptococcus* genera. The claim broadly encompasses species of Streptococcus. The claimed methods of treating or preventing Streptococcus infecntions includes *S. mutans, S. suis, S. dysgalactiae* and *S. pyogenes* just to name a few. The specification only contemplates the treatment or prevention of *Streptococcus pneumoniae* infections and not all *Streptococcal* infections. For example, Oli et al *(Infection and Immunity, December 2004, p. 6951-6960)* teach that *Streptococcus mutans* is the predominant etiologic agent of dental caries (page 6951). Swildens et al *(Veterinary Microbiology 103, 2004, 29-33)* teach that *Streptococcus suis* causes bacterial infections in pigs (see the Abstract). Bolton et al *(Can J. Microbiol., June 2004, 50(6):423-32)* teach that *Streptococcus dysgalactiae* is a significant pathogen associated with bovine mastitis (see the Abstract). Okamoto et al *(Vaccine 22 (2004) 2887-2893)* teach that *Streptococcus pyogenes* (Group A streptococci (GAS)) causes a variety of diseases including pharyngitis, impetigo and acute rheumatic fever (see page 2887). One of skill in the art would not expect the claimed vaccines comprising *Streptococcus pneumoniae* polypeptides to be effective in treating or preventing infections caused by *Streptococcus mutans, Streptococcus suis, Streptococcus dysgalactiae* or *Streptococcus pyogenes* to name a few species of *Streptococcus* encompassed by the broadly claimed method. One of skill in the art could reasonably conclude by what is disclosed in the instant specification that claimed vaccines would provide protection against all streptococcus infections. One of skill in

the art would require guidance, in order to make or use the claimed vaccine in a manner reasonable in correlation with the claims.

Factors to be considered in determining whether undue experimentation is required, are set forth in In re Wands 8 USPQ2d 1400. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims.

Applying the above test to the facts of record, it is determined that 1) no declaration under 37 C.F.R. 1.132 or other relevant evidence has been made of record establishing the amount of experimentation necessary, 2) insufficient direction or guidance is presented in the specification with respect to selecting other polypeptides having claimed functional features and providing a vaccine comprising the *S. pneumoniae* polypeptides that provides protection against all streptococcal infections, 3) the relative skill of those in the art is commonly recognized as quite high (post-doctoral level). One of skill in the art would require guidance, in order to make or use the claimed *S. pneumoniae* polypeptides, vaccine and method of treating and preventing all Streptococcal infections that are in a manner reasonable in correlation with the claims. Without proper guidance, the experimentation is undue. It should be remembered that 35 U.S.C. 112, first paragraph requires that Applicants teach how to "make and use" the claimed invention not how to "find" polypeptides with the claimed biological activity. A structural description is required. Therefore, one skilled in the art would require the

structure of the polypeptides to used in the vaccine as well as a demonstration that the claimed vaccines provide protection against all streptococcal infections in order to successfully practice (make and use) Applicant's invention as required under 35 U.S.C. 112, first paragraph.

### *Status of Claims*

8. No claims allowed. Claim 19 appears to be free of the cited prior art.

### *Conclusion*

9. Any inquiry of the general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308–0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Office Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for the Group 1600 is (703) 872-9306.

Any inquiry concerning this communication from the examiner should be directed to Vanessa L. Ford, whose telephone number is (571) 272-0857. The examiner can normally be reached on Monday – Friday from 9:00 AM to 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached at (571) 272-0864.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov./>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Vanessa L. Ford
Biotechnology Patent Examiner
November 22, 2004

NITA MINNIFIELD
PRIMARY EXAMINER